Wilson’s disease: aids to interpretation of simple specific investigations. I. B. Sardharwalla, E. M. Hammond, and A. Sass-Kortsak. Willink Biochemical Genetics Laboratory, Royal Manchester Children’s Hospital, Pendlebury, Manchester, and Research Institute, the Hospital for Sick Children, Toronto, Canada.

Wilson’s disease, a rare disorder of copper metabolism, can now be effectively treated with D-penicillamine. However, before committing the patient to life-long treatment, an unequivocal diagnosis must be made. In the absence of Kayser-Fleischer rings, a pathognomonic sign of this condition, a number of simple investigations related to copper metabolism aid the diagnosis. For reliable interpretation determinations should be undertaken by laboratories experienced in handling trace metals. The tests are (1) serum copper and caeruloplasmin levels which are reduced in Wilson’s disease (normal serum copper 67–149 µg/100 ml; serum caeruloplasmin 20–7–40·2 mg/100 ml. However, 4% of patients have normal values and 10% of heterozygotes may have levels below normal. Certain physiological and pathological states may also influence levels. A simple calculation of noncaeruloplasmin-bound copper, increased in Wilson’s disease, will help to resolve the confusion. (2) Urinary excretion of copper in symptomatic patients is almost always increased to >100 µg/24 h (normal <40 µg/24 h). For this measurement meticulous care must be taken in avoiding copper contamination during urine collection and subsequent handling of specimens. (3) After oral administration of 1g penicillamine/day the urinary excretion of copper increases to >1000 µg/24 h, whereas in normal subjects and heterozygotes it does not exceed 800 µg/24 h.

The summation of these parameters will provide a confident diagnosis of Wilson’s disease in the majority of cases, thus avoiding less favoured procedures such as liver biopsy and radioactive copper studies.

Histidinaemia: experience in treatment and follow-up of 21 cases. E. H. Dryburgh, I. B. Sardharwalla, and G. M. Komrower. Willink Biochemical Genetics Laboratory, Royal Manchester Children’s Hospital, Pendlebury, Manchester.

Histidinaemia is a rare inborn error of amino acid metabolism. A high proportion of the first (approximately 50) patients described with the condition were retarded in either mental or speech development. Since population screening in the newborn has become widespread, however, fairly large numbers of affected elder sibs of histidinaemic probands have been discovered who show normal development. Opinions differ widely as to whether or not the disease should be treated.

In the Manchester region during the past 5 years 12 cases have been discovered from 320 000 infants screened. 4 further cases have been found among sibs of the probands. One case was discovered during the investigation of developmental delay.

Our policy has been to treat those cases found on the screening programme with low histidine diet, using Cow & Gate HP2 Formula, for the first 2 years of life. The affected sibs have not been treated. There has been regular follow-up to assess control, physical and psycho-motor development. There have been very few dietary difficulties. The children have progressed well. Intelligence quotients range from 87–132 (mean 109). Speech in all cases is normal. An interesting observation is that the children grow very well while on the diet (mean height centile 75th).

We think that if a dietary policy is to be adopted good control is fairly easy to achieve and the children do not suffer nutritionally. We feel that a collaborative study should be launched to discover whether dietary treatment is necessary.


Dialysis and transplantation have improved the long-term outlook for children with chronic renal failure, and consequently bone disease has assumed more importance. The aim of this study is to explore means of detecting bone disease at an early stage in the hope of preventing serious complications by early treatment and possibly in the future by preventive measures.

The results in the first 19 children studied showed a high incidence of osteodystrophy radiologically (9 out of 19); all the children with radiological evidence of osteodystrophy had raised immunoparathyroid hormone (iPTH). In addition, 6 children had raised iPTH levels with normal bone x-rays and in most of these there was histological evidence of bone disease. Only 4 children had normal iPTH levels and all these had normal bone x-rays, normal bone biopsies, and mild
renal failure. Serum 25-hydroxycholecalciferol levels correlated with the level of vitamin D intake and not with the degree of renal failure or the type of bone disease.

More than 30 children have now been studied and these results confirm that development of clinical and radiological abnormalities cannot be predicted from the severity or duration of renal failure. They also emphasize the value of monitoring the serum iPTH levels in that when abnormalities were recognized, the serum iPTH was invariably increased and usually markedly increased.

Management of severe secondary hyperparathyroidism is difficult and in an effort to prevent this complication, therapy is now being given to these children with normal x-rays but increased serum iPTH, with the aim of maintaining the serum iPTH within the normal range. Therapy for the children with rickets also poses some problems. Vitamin D can be used successfully but we have found this therapy difficult to manage particularly in children on haemodialysis. 1α-hydroxycholecalciferol is an alternative, and initial experience with this was discussed.


The association of sexual precocity and juvenile hypothyroidism, though long recognized, has been considered a rare and paradoxical clinical entity. However, a study of 54 children (38 girls, 16 boys) with primary hypothyroidism showed that 31 (22 girls, 9 boys) had evidence of isosexual maturation that was advanced in relation to the 'maturational' (bone) age. Clinical features in the girls included breast development and oestrogenization of the vaginal mucosa, and in the boys testicular and penile enlargement, frequently without other evidence of peripheral androgenic effects. Development of pubic hair was relatively delayed in both sexes. Associated features included, in some girls, hypertrophy of the labia minora, vaginal bleeding, and galactorrhoea and, in some boys and girls, enlargement of the sella turcica. Serum gonadotrophin concentrations were increased in relation to maturational age, follicle stimulating hormone in all of 13 and luteinizing hormone in 10 of 17 patients studied. The changes were reversed by administration of thyroxine.


Scalp hair as an aid to clinical diagnosis in children. D. Baum and D. Harris. Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Headington, Oxford.

We have studied scalp hair from children with a variety of clinical conditions using two main methods.

Light microscopy. By ordinary light microscopy we have been able to identify changes in hair shaft diameter corresponding to abrupt changes in nutritional status.

Scanning electron microscopy. By this method we have studied the surface anatomy of hair from children with a variety of clinical conditions. Examples were shown of appearances which we consider possibly pathognomonic of hypothyroidism, homocystinuria, and cartilage hair hypoplasia. An example was shown of hair damage from cytotoxic drug therapy in which a pregnant mother was treated during pregnancy and in which her hair showed signs of cytotoxicity but fetal hair sampled at birth from the normal infant showed no signs of cytotoxicity, suggesting that the drug had not crossed the placenta.


Meningitis may be complicated by vascular lesions, as has been shown histologically and by angiography. In a preliminary study, fibrin degradation products (FDP) were found in the cerebrospinal fluid (CSF) of children with meningitis (Brueton et al., 1974). It was not established whether they originated from the cerebral circulation and leaked across a damaged blood-brain barrier, or whether they were produced by the digestion of fibrin deposited on the meninges. The present report describes an investigation of coagulation and fibrinolytic proteins in the CSF and blood in 47 patients undergoing diagnostic lumbar puncture. 18 had bacterial or viral meningitis, 10 had acute lymphatic leukaemia, 5 had febrile convulsions, and 14 meningitis or cerebral dysfunction. In 17 of the 18 patients with meningitis there was an increase in low molecular weight (MW) FDP in the CSF, usually accompanied by plasminogen (MW 89 000), protein, and Factors VII (MW 60 000) and IX (MW 50 000), but not by higher MW, FDP, or fibrinogen (MW 340 000). Only 6 of these patients had detectable serum FDP. In the control group of 29 patients without infection, no FDP or low MW coagulation proteins were present in the CSF.

These findings are consistent with the presence of FDP arising locally within the cerebral circulation and leaking across a damaged blood-brain barrier. FDP are also found in the CSF in subarachnoid haemorrhage, but have not been studied in neonatal intraventricular haemorrhage. Their diagnostic value and origin require further studies in these conditions.

REFERENCE


Enteropathogenic strains of Esch. coli (EPEC), associated with sporadic and epidemic cases of infantile gastroenteritis are, at present, identified by agglutination tests which detect surface antigenicity. Infection with EPEC strains may, however, be asymptomatic and the significance of their isolation is often difficult to evaluate. More recently strains of Esch. coli have also been associated with some cases of acute gastroenteritis in adults. The pathogenesis of the disease has been ascribed to the action on the small intestine of an enterotoxin produced by the organism, and two forms, a heat labile (LT) and a heat stable (ST) type, have been described. The role of enterotoxin-producing organisms in infancy has not yet been studied. The major obstacle has been the lack of a suitable reliable test system, as conventional animal methods are time consuming and poorly reproducible in determining toxin production by infant strains.

Tissue culture methods recently described for investigating the pathophysiology of enterotoxin, and for the detection of toxin producing strains in adults obviate the need for animal experiments. In the present study a fibroblast cell line of human embryo lung was used. Readily distinguishable morphological changes were shown with LT toxin preparations. Production of LT toxin by 52 EPEC strains from an unselected group of children was studied.

**Respiratory function in neuromuscular disorders.** M. T. Cunningham, S. Godfrey, and V. Dubowitz. Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London.

A comprehensive range of lung function studies is being applied to children with various neuromuscular problems to delineate whether respiratory involvement is due to mechanical impairment, ventilation-perfusion inequality, or defective central control. The restrictive defect in children with Duchenne muscular dystrophy correlates well with functional disability, the most severely affected children having values for FEV₁ and FVC of 50–65% expected. In other myopathies and dystrophies restrictive defects have been shown, but severity does not correlate with functional disability. In spinal muscular atrophy those with the Kugelberg-Welander form, i.e. mildest form, have normal lung function, but restrictive defects have been shown in the intermediate form in 2 children both of whom have scoliosis.

Central control has been evaluated using the rebreathing method of Read and results in 24 children fall within the normal range. Of 16 children with restrictive defects mean slope (S) was 1.84 l/min per mmHg ± 1.2 (2SD), a similar range to a control group of 30 schoolchildren with mean S 1.6 l/min per mmHg. One child with nemaline myopathy who presented in respiratory failure had an abnormally flattened response, S = 0.07 l/min per mmHg, initially and 0.4 l/min per mmHg at follow-up. Simple progressive exercise tests in 6 children with restrictive defects have shown that % work load achieved is less than % MVV achieved. Heart rate was appropriate for work load.

**Induction—Theoretical calculation of risk to the neonate.** J. I. Cater. Department of Child Health, University of Dundee.


A retrospective survey of necropsies performed on 272 infants with birthweights between 800 and 2500 g in 1956–1959 (before bicarbonate and THAM), and on 125 infants in 1971–1974 (during bicarbonate and THAM) was made. Necropsy rates were 92 and 88% and total live births in that weight range were 1118 and 1227 respectively. The incidence of intraventricular haemorrhage (IVH), was 49/1000 in 1956–1959 compared with 41/1000 live births (800–2500 g) in 1971–1974, though the incidence of hyaline membrane disease (HMD) had fallen from 79/1000 to 45/1000 live births over the same period.

From the 1971–1974 series 39 infants with HMD and IVH were compared with 16 infants with HMD alone. No significant differences were found relating to obstetric history, asphyxia at birth, or other perinatal events, and there were no differences in mean arterial blood gas values or in the incidence of coagulation defects. Pulmonary interlobular lymphatic diameters were greater in IVH cases (58 ± 4 ± 21.3 μm in HMD; 45 ± 7 ± 11.6 μm in IVH). The highest plasma sodium concentration recorded in 9 infants with HMD alone (146 ± 4 mmol/l) was not significantly different from that in 37 infants with IVH (144 ± 9 mmol/l). Significantly larger total quantities of sodium bicarbonate were given to IVH infants and there was a correlation between the amounts of bicarbonate infused and the maximum plasma sodium (r = 0.57; P < 0.001). In 19 infants where the onset of IVH could be recognized with some certainty buffer had not been given in the preceding 6 hours, but alkali injection frequently followed clinical deterioration. These findings do not suggest an important role for sodium bicarbonate therapy in the pathogenesis of IVH.

**Phototherapy and oxygen consumption in the neonatal period.** O. R. C. Smales. Department of Child Health, University of Nottingham.

**Pupil size at birth.** P. C. Etches. Department of Paediatrics, The Radcliffe Infirmary, Oxford.

It is recognized that the presence of fixed dilated pupils in children and adults points to severe cerebral injury. The present study set out to test whether pupil diameter at birth could be used as a measure of birth asphyxia. 97 babies were assessed immediately after birth. Pupil diameter was estimated using a hand ‘pupilmeter’ at an average postdelivery time of 5 minutes. 53 babies were considered free from birth asphyxia (Apgar > 8 at 1 minute and > 9 at 5 minutes and required no form of resuscitation). These infants
had a mean pupil diameter of 2·2 mm. 13 babies were considered to be severely asphyxiated (Apgar < 3 at 1 minute and mean Apgar at 5 minutes of 5; and required intermittent positive pressure ventilation for more than 5 minutes after birth and/or received intravenous sodium bicarbonate). These infants had a mean pupil diameter of 3·4 mm. This is significantly larger than the pupil diameter of the normal group.


A method is described of measuring the volume of a baby using Boyle’s law. The baby is placed in one of two identical sealed boxes and an identical volume of air is pumped in and out of each box in a sinusoidal fashion. The differential pressure between the boxes is analysed by Fourier analysis which removes artefact due to the baby’s movement and breathing. A slow and critically adjusted leak between the boxes compensates the pressure changes of temperature and water vapour generated by the baby. It is thus possible to determine the baby’s volume correlated to within a few ml by plotting the results obtained with the baby on a calibration curve made using objects of known volume.

In the first 48 hours after birth there are abrupt changes in the density of babies, presumably related to changes in body water. (An increase in body fat decreases the body density and an increase in body water moves the specific gravity closer to that of 1·000.) In a small number of babies so far studied it appears that in the first day small-for-dates babies are more dense than preterm babies, who in turn are more dense than term babies.

Fetal exposure to 1:8 dihydroxyanthraquinone. A. W. Blair, M. Burdon, J. Powell, M. Gerrard, and R. Smith. Department of Paediatrics, Victoria Hospital, Kirkcaldy and Department of Biochemistry, University of St. Andrews.

Laxative taken in pregnancy is relatively common and a survey of 160 consecutive maternity cases showed that 24 mothers had taken a laxative of the anthraquinone type at some stage during the pregnancy. 1:8 dihydroxyanthraquinone was given to patients due to induction within 24 hours. Using a fluorescence assay, the substance was measured in the maternal urine and amniotic liquor at induction and in the first urine obtained from the baby. The results suggested that the substance is absorbed from the maternal gut, crosses the placenta, and is excreted via the fetal kidney into the liquor. In both mothers and babies most of the drug appearing in the urine was present as the glucuronide, the proportion being slightly less in the babies. There was no case of meconium staining observed in any of the babies born in this series and fetal catharsis from maternal exposure to the drug in therapeutic amounts does not seem to be a problem to the obstetrician.

Skinfold thickness as an indication of intrauterine malnourishment. J. R. Oakley and J. Parsons. Department of Child Health, The Children’s Hospital, Sheffield.

‘Light-for-dates’ infants are subject to neonatal hypoglycaemia, and show an initially rapid postnatal growth velocity. Some term infants, birthweight > 2·5 kg, seem to exhibit these same characteristics; and many of these appear clinically to have suffered from intrauterine malnourishment. The appearance of these infants is related to the amount of subcutaneous fat present, and this may be measured using skinfold calipers. Skinfold thickness was used in this trial to indicate intrauterine malnourishment, and to predict postnatal growth velocity.

500 infants of consecutive deliveries (excluding premature and severely ill infants) were measured at birth for triceps and subcapular skinfold thickness. Skinfold thickness was plotted against the appropriate birthweight, and centile charts prepared for each sex. It was shown that infants falling below the 50th centile on the chart at birth had a significantly higher weight gain over the first 6 weeks of life than those above the 50th centile. This trend was present at 3 days of life. The difference in weight gain is related to differences in skinfold thickness; and not to differences in birthweight.

Further studies are being carried out to ascertain whether the chart can be used to predict hypoglycaemia, and also the eventual stunting of somatic growth, often seen in ‘light-for-dates’ infants. The practical applications of this study are to show those infants who are exhibiting catch-up growth over the first 6 weeks of life, rather than a truly excessive weight gain. It may also be possible to identify those infants whose birthweight is > 2·5 kg at birth but who are prone to neonatal hypoglycaemia.

Single umbilical artery as an indication of renal abnormalities. I. B. Houston. Department of Child Health, Royal Manchester Children’s Hospital, Pendlebury, Manchester.